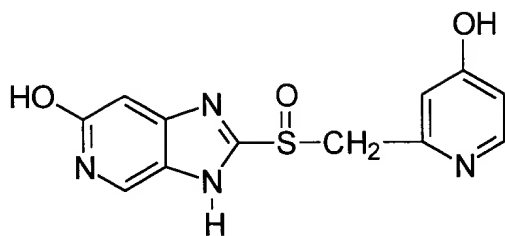
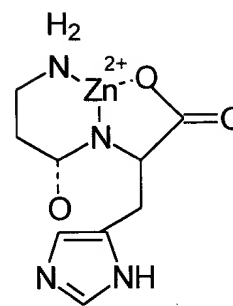


or of general formula II or III,



II



III

and

- at least one pharmaceutically acceptable excipient selected from the group which includes: a binder, an alkaline reaction compound, surface-active agents, a filling material and disintegrating-swelling excipients;

b) drying the active layer formed during said spraying to form a charged nucleus; and

c) coating the charged nucleus by spraying a solution which contains an enteric coating polymer with at least one pharmaceutically acceptable excipient selected from the group comprising: a plasticizer, a surface-active agent, a pigment and a lubricant, to form an gastro-resistant external coating layer.

### REMARKS

Claim 14 has been cancelled. Upon review it was noted that Formula 1 had inadvertently been omitted from originally filed claim 14. Claim 14 has been replaced by a new claim 34 that is identical to claim 14 but for the inclusion of the compound of Formula 1 and using singular language ("nucleus") in place of plural language ("nuclei") which had been used in claim 14.

Claims 15 to 25 and 30-33 have been amended to correct the dependency.

Claims 1-4, 6-16 and 18-33 were rejected under 35 U.S.C.103 as unpatentable over European Patent Application 519144 to Tanberk et al. (Tanberk). Claims 1-4, 6-16 and 18-33 were rejected under 35 U.S.C. 103(a) as unpatentable over European Application 773025 to Ballester Rodes et al. (Ballester Rodes). Claims 1-33 were rejected under 35 U.S.C. 103(a) as unpatentable over Tanberk or Ballester Rodes in view of European Patent Specification 244380 to Lövgren et al. (Lövgren). It is submitted these rejections were improper and should be withdrawn.

The Examiner states that in each of Tanberk and Ballester Rodes, an inert core is coated with a layer of omeprazole or the benzimidazole compound followed by another coating of a water soluble layer or protective coating. The Examiner candidly admits that in each of Tanberk and Ballester Rodes, the enteric coating is the third layer which is applied over the protective layer. The protective layer has been coated over the layer containing the active ingredient and that active ingredient containing layer has been coated on to the inert sugar or starch core.

As also admitted by the Examiner, the present invention is directed to a pharmaceutical composition wherein an inert nucleus is coated by a soluble layer having the active ingredient or a layer which disintegrates rapidly in water and that active ingredient containing layer is in turn coated by the outer or gastro-resistant outer coating. Thus, as recognized by the Examiner, the now claimed invention recites a composition with a two layer coating rather than a three layer coating and Tanberk and Ballester Rodes each disclose a three layer coating.

The Examiner asserts that the product and process taught by each of Tanberk and Ballester Rodes render the now claimed subject matter obvious because one of ordinary skill in the art would have been motivated to use the teachings of Tanberk or Ballester Rodes to create a successful coated particle pharmaceutical formulation with the expected result of having a

successful antiulcer formulation and thus the invention as a whole would have been *prima facie* obvious.

It is respectfully submitted that the rejections are in error.

The references provide no motivation to alter the formulations or pellet structure disclosed therein. To the contrary, each of the references alone and in combination teaches away from the now claimed invention.

There is no suggestion in either of Tanberk or Ballester Rodes that a two-layer structure could be employed when the active ingredient is omeprazole or a similar benzimidazol.

The Examiner's explanation does not provide motivation and does not establish on the record how the cited references show or suggest the now claimed invention. What in any of the references provides motivation to remove one of the layers that is required in each of those references. In effect, the Examiner has modified each of the references. However, without art provided motivation for such a modification, this is improper. See, In re Hummer, 113 U.S.P.Q. 66, 69 (CCPA 1957)(Prior patent is reference only for what it clearly shows or discloses or suggests; it is improper use of patent to modify its structure to one which it does not suggest).

There is no disclosure in any of the references that suggests that a two-layer structure would be successful. In this regard, the Examiner is in effect ignoring what each of the references considers to be an essential ingredient or feature of the respective invention disclosed therein. Thus, the Examiner has improperly attempted to modify those references and in doing so has postulated a formulation or structure which would undermine the very purpose of the invention disclosed in each of those references. This is again improper under 35 U.S.C. 103 see In re Ratti 123 U.S.P.Q. 349, 352 (CCPA 1959).

The combination of the Lövgren reference with either Tanberk or Ballester Rodes does not overcome the teachings of either of the references which discloses a three-layer structure.

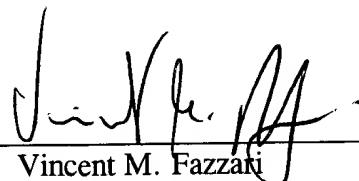
In Lövgren, the active ingredient can be in the core. However, it is clear from Lövgren that there must be a separating layer between the active ingredient (omeprazole) and the outer enteric coating layer. The purpose of the separating layer is to avoid contact of the acid labile active ingredient with the enteric coating layer which generally is composed of one or acidic-like materials. Lövgren teaches that the alkaline containing separating layer between the active ingredient and the enteric coating layer will protect the active ingredient from the acidic properties of the enteric coating or outer layer. Thus, Lövgren also teaches away from the now claimed subject matter.

Submitted herewith are certified copies of Priority Documents Nos. 97011816 and 9900157.

In view of the foregoing, reconsideration and allowance of the application with claims 1-13 and 15-34 are earnestly solicited.

Respectfully submitted,

COHEN, PONTANI, LIEBERMAN & PAVANE

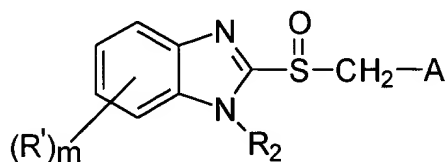
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Dated: June 18, 2001

Version with Markings to Show Changes

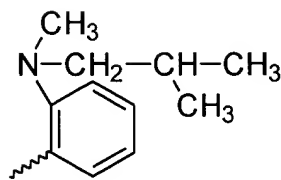
In the Claims:

1. (Amended) An oral pharmaceutical preparation comprising:
  - a) an inert nucleus;
  - b) a soluble active layer or layer which disintegrates rapidly in water, made from a single aqueous or hydroalcoholic solution-suspension which comprises:
    - an active ingredient of anti-ulcer activity of general formula I

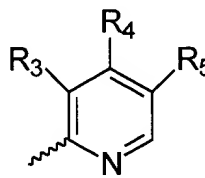


wherein:

A is:



or



in which: R<sup>3</sup> and R<sup>5</sup> are the same or different, and may be hydrogen, alkyl, alkoxy, or alkoxyalkoxy;

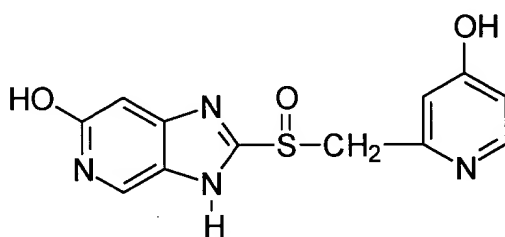
R<sup>4</sup> is hydrogen, alkyl, alkoxy which can optionally be fluorated, alkoxyalkoxy, or alkoxycycloalkyl;

R<sup>1</sup> is hydrogen, alkyl, halogen, cyano, carboxy, carboalkoxy, carboalkoxyalkyl,

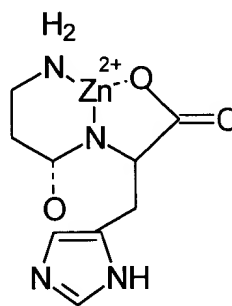
carbamoyl, carbamoylalkyl, hydroxy, alkoxy, hydroxyalkyl, trifluoromethyl, acyl, carbamoyloxy, nitro, acyloxy, aryl, aryloxy, alkylthio or alkylsulphinyl;

$R^2$  is hydrogen, alkyl, acyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonilmethyl, alkoxycarbonilmethyl or alkylsulfonil; and, m is a whole number from 0 to 4;

or of formula II or III,



II



III

and

- at least one pharmaceutically acceptable excipient selected from the group which includes: a binder, an alkaline reaction compound, a surface-active agent, a filling material and a disintegrating-swelling excipient; and

c) a gastro-resistant outer coating on the layer of (b), wherein said gastro-resistant out coating is made from a solution which includes:

- an enteric coating polymer; and

- at least one excipient chosen from the group which includes: a plasticizer, a surface-active agent, a pigment and a lubricant.

15. (Amended) The process of claim [14] 34 further comprising drying the coated charged [nuclei] nucleus.

16. (Amended) The process of claim [14] 34 wherein said binder in said aqueous or hydroalcoholic solution-suspension is selected from the group consisting of saccharose, starch, methylcellulose, CMC, HPC, HPMC, polyvinyl pyrrolidone (PVP), dextrin or gum arabic, either alone or mixed, dissolved in water, ethanol or a mixture of both at 50% (v/v).

17. (Amended) The process of claim [14] 34 wherein said compound of alkaline reaction in said aqueous or hydroalcoholic solution-suspension is selected from the group consisting of trisodium phosphate, disodium phosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, aluminium hydroxide, carbonate, phosphate or citrate of aluminium, calcium, sodium or potassium, and the mixed compounds of aluminium/magnesium  $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$  or  $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$  and amino acids with alkaline reaction.

18. (Amended) The process of claim [14] 34 wherein said surface-active agent present in said aqueous or hydroalcoholic solution-suspension is selected from the group consisting of sodium lauryl sulphate, polysorbate, poloxamer or other ionic and non-ionic surface-active agents.

19. (Amended) The process of claim [14] 34 wherein said filling material in said aqueous or hydroalcoholic solution-suspension is selected from the group consisting of lactose, starch, saccharose and microcrystalline cellulose.

20. (Amended) The process of claim [14] 34, wherein said disintegrating-swelling excipient in said aqueous or hydroalcoholic solution-suspension is selected from the group consisting of starch, CMCCa, sodium glycolate starch and L-HPC.

21. (Amended) The process of claim [14] 34 wherein said enteric coating polymer in said external gastro-resistant coating is selected from the group consisting of methyl cellulose, HEC, HBC, HPMC, ethyl cellulose, HMC, HPC, polyoxyethylene glycol, castor oil, cellulose phthalic acetate, phthalate of HPMC, succinate acetate of HMC, sodium carboxymethylamylopectin, chitosan, alginic acid, carrageenans, galactomannons, tragacanth, shellac, agar-agar, gum arabic, guar gum, xanthan gum, polyacrylic acids, methacrylics and their salts, PVA, polyethylene and polypropylene oxides and mixtures thereof.

22. (Amended) The process of claim [14] 34 wherein said plasticizer in said external gastro-resistant coating is selected from the group consisting of TEC, PEG, cetyl and stearyl alcohol.

23. (Amended) The process of claim [14] 34 wherein said surface-active agent in said aqueous or hydroalcoholic solution-suspension is selected from the group consisting of sodium lauryl sulphate, polysorbate and poloxamer.

24. (Amended) The process of claim [14] 34 wherein said pigment in said external gastro-resistant coating layer is selected from the group consisting of titanium dioxide and iron sesquioxide.

25. (Amended) The process of claim [14] 34 wherein said lubricant in said external gastro-resistant coating layer is selected from the group consisting of talc, magnesium stearate and glyceryl monostearate.

30. (Amended) The process of claim [14] 34 wherein the filling material is selected from the group consisting of mannitol, sorbitol or gelatin.

31. (Amended) The process of claim [14] 34 wherein the alkaline reacting compound is selected from the group consisting of sodium, potassium, aluminum or calcium acetate; sodium, potassium, aluminum or calcium glycerophosphate; (tris)-hydroxymethylaminemethane (tromethamine); N-methylglucamine, 2-amine-2-methyl-1, 3-propanediol; 2-amine-2-methyl-1propanole; sodium, potassium, magnesium, calcium, aluminum or aluminum hydroxide salts of aminoacids like lysine, glutamic acid, glycine or pyrimidinecarboxylic acids, like nicotinic acid, salts derived from organic or weak inorganic acids and bases like guanidine and basic aminoacids like arginine, histidine, lysine and triptophane.

32. (Amended) The process of claim [14] 34 wherein the enteric coating

polymer is selected from the group consisting of HPMC acetate succinate, polyvinyl acetate phthalate and, cellulose acetate trimethylate.

33. (Amended) The process of claim [14] 34 wherein the plasticizer is selected from the group consisting of diethyl phthalate, dibutyl phthalate, dimethyl phthalate, dioctyl adipate, dioctyl phthalate, dioctyl terephthalate, butyloctyl phthalate, triethylene glycol di-2-ethylhexanoate, trioctylmethyle, glyceryl triacetate, glyceryl tripropionate and, 2,2,4-trimethyl-1, 3-pentanedioldiisobutyrate.